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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/787,559	Applicant(s) KRAMER ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-28 is/are pending in the application.

4a) Of the above claim(s) 1,7,12-16,19,21-23 and 25-28 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 2-6,8-11,17,18,20 and 24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *attachment* .

DETAILED ACTION

Claims 1-28 are pending in the application.

Election/Restrictions

1. Applicant's election without traverse of Group II (claims 2-6, 8-11, 17, 18, 20 and 24) in Paper No. 10 is acknowledged. Claims 1, 7, 10-16, 19, 21-23 and 25-28 are drawn to non-elected subject matter and are withdrawn from consideration.

Specification

2. The disclosure is objected to because of the following informalities: the specification is replete with typographical errors. Specifically, it appears that the quotation marks were misprinted throughout the specification. For example, see the last word on page 5.

Appropriate correction is required.

Sequence Compliance

The CRF that was submitted in response to the Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures contained non—ASCII "garbage" at the end of the files. The "garbage" was deleted from the files and the sequence listing was then entered.

However, the application still fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence

Disclosures. Specifically, in the last paragraph on page 16, the sequences of two PCR primers are disclosed. SEQ ID Nos. are required for the sequences disclosed on page 16 (see 37 C.F.R. §§ 1.821-1.825). The sequence compliance issues mentioned do not preclude initial examination of the instant application. However, in response to this Office Action, Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2-6, 8-11, 17, 18, 20 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to an isolated nucleic acid that encodes a protein, which is functionally identical to a protein that occurs naturally in human keratinocytes. The limitation of the claims create genus situations where the number of nucleic acids potentially comprises millions or more different species of nucleic acids encoding proteins functionally identical to pKe#122. For example, in a minimal way, Applicant has only disclosed the protein named pKe#122, which is encoded by SEQ ID No. 1 or SEQ ID No. 4. As written, the claims incorporate any mutation in the nucleic acid encoding pKe#122 (whether the mutation is functional or not), including point mutations, substitutions, inversions, deletions and duplications that result in proteins functionally identical to pKe#122, a genus that encompasses possibly

millions of different molecules. Thus, applicant has express possession of only two species (SEQ ID No. 1 and SEQ ID No. 4) in a genus which comprises possibly hundreds of millions of different possibilities. The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the sequences that are critical to any functionally identical molecule are disclosed. Additionally, the elements or attributes not critical for to any functionally identical molecules are not disclosed. Further, there is not any methodology presented to determine such common elements or attributes.

With regard to the written description, all of the claims encompass sequences different from those disclosed in the specific SEQ ID Nos. which include modifications by permitted by the "functionally identical" language for which no written description is provided in the specification.

> It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only the sequences of the disclosed SEQ ID Nos. are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of any nucleic acids encoding molecules functionally identical to pKe#122.

5. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claim is drawn to use of a sense or antisense oligonucleotide for the diagnostic and/or therapeutic treatment of dermatological diseases or for the cosmetic treatment in particular of the epidermis. Therefore the nature of the invention encompasses gene therapy, including antisense oligonucleotide therapy.

The breadth of the claims

The breadth of the claim is very broad. For instance, the claim encompasses a DNA or RNA oligonucleotide that is useful for the diagnosis and/or treatment of any dermatological disorder or that is useful for any cosmetic treatment in any species of animal.

The unpredictability of the art and the state of the prior art

At the time of filing the relevant prior art regarded gene therapy and antisense oligonucleotide gene therapy as highly unpredictable. With regard to oligonucleotides as therapeutic reagents, the bulk of the art indicates the difficulty in utilization of antisense therapies. Probst et al. (TIGs Vol. 12(8):290-291; 1996) notes,

> "The mechanism of antisense oligonucleotide action is poorly understood and relies primarily on speculation and, as recently described in Nature Medicine and Science, seems to have 'growing pains' due to the lack of knowledge regarding antisense action. Improper use of molecular terminology (ref omitted) will also lead to misunderstandings, as will incompletely analyzed cellular and molecular effects evoked by antisense oligonucleotides (page 90, column 1, third paragraph)".

Regarding gene delivery in vivo, Harris et al. (TIGs Vol. 12(10):400-405; 1996) stated that,

> "The major hurdle now is the poor efficiency of gene delivery in vivo with the gene transfer technology presently available, but we anticipate that this will be overcome by further modifications of viral vectors and the development of synthetic systems combining the best elements of a variety of vectors (page 405)".

The prior art also supports the unpredictable nature of the art. It is unpredictable which formulations, compounds and delivery modes will function in an in vivo setting. This unpredictability is evidenced in a report in Science (Vol. 269:1050-1055) which states that, "So

far, there has been no unambiguous evidence that genetic treatment has produced therapeutic benefit (page 1050, column 1)".

There appears to be no prior art on the nucleic acid molecules encoding pKe#122, the pKe#122 protein itself, or on the function of the pKe#122 protein. There is no recognition in the prior art that pKe#122 is involved in any way in any dermatological disorder. Furthermore, there is no evidence in the prior art that oligonucleotides which hybridize to SEQ ID No. 1 or SEQ ID No. 4 would be useful in diagnosing or treating any dermatological disorder or that the oligonucleotides would be useful for cosmetic treatment as the protein encoded by SEQ ID No. 1 and SEQ ID No. 4 (pKe#122) had not been associated with any dermatological disorder.

Working Examples and Guidance in the Specification

The specification has only one working examples, of oligonucleotides that hybridize to SEQ ID No. 1 or SEQ ID No. 7. The working example (Example 6 in the instant specification) is an experiment where cells were treated in vitro with antisense oligonucleotides. The treated cells displayed an altered morphology which allowed the applicants to conclude that "cells treated with pKe#122-specific antisense-oligonucleotides show an increased tendency toward differentiation (see page 20, first paragraph)." However, there are no working examples of in vivo use of the antisense oligonucleotides, the results of which are critical to determining the therapeutic effectiveness of the reagents. There are also no examples demonstrating the accuracy of the oligonucleotides in diagnosing any disease/disorder. There are no working examples or guidance in the specification on methods of using the oligonucleotides for cosmetic treatment.

Therefore, it is unpredictable that the oligonucleotides could successfully be used to diagnose and/or treat any dermatological disorder, or that the oligonucleotide could be successfully used in cosmetic treatment.

Quantity of Experimentation

The quantity of experimentation required is extremely large since pKe#122 (the protein encoded by SEQ ID No. 1 and SEQ ID No. 4) has not been associated with any dermatological disorder. Therefore, it must first be determined if pKe#122 is associated with a dermatological disorder. If pKe#122 is not associated with any dermatological disorder, then the oligonucleotides would not be useful in diagnosing and/or treating any dermatological disorder. Determining if pKe#122 is involved in dermatological disorders would require testing for the alteration of pKe#122 in every possible dermatological disorder. The alterations could include overexpression, loss of expression, or mutations that increase or decrease the activity of pKe#122. Once it was determined that pKe#122 was associated with a dermatological disorder, the efficacy of the oligonucleotide in treating the disorder would have to be tested, a process that includes in vitro experiments, testing in animals, and finally clinical studies in human subjects. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 18 is rejected under 35 U.S.C. 112, first paragraph because it provides for the use of sense or antisense oligonucleotides, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

8. Claims 8, 9, 17 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 recited the phrase "Recombinant DNS vector molecule". It appears that the term "DNS" is a typographical error and should read "DNA". However, the term "DNS" could be construed to mean a specific vector. Therefore, the term "DNS" is unclear and renders claims 8 and 9 indefinite.

Claims 17 and 24 recite the phrase, "Reagent for the indirect detection of a protein that occurs in human keratinocytes and is increasingly expressed in activated keratinocytes". This phrase is unclear because it could be interpreted to mean that the reagent is increasingly expressed in activated keratinocytes or that the protein is increasingly expressed in activated keratinocytes. Therefore, claims 17 and 24 are indefinite.

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 18 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 2, 3, and 5 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention.

Claim 2 recites, "Isolated nucleic acid that encodes a protein, which is functionally identical to a protein that occurs naturally in human keratinocytes... **or** a nucleotide sequence that hybridizes wholly **or in part** with one of these aforementioned nucleotide sequences." Therefore, the claim encompasses any nucleotide sequence that hybridizes to SEQ ID No. 1 or SEQ ID No. 4. Random hexanucleotides were available for sale as early as 1997 (see 1997 Boehringer Mannheim Catalog, page 95). The hexanucleotide mix available comprised, "mixture of hexamer nucleotides of all possible sequences for random primed DNA labeling." Therefore, there existed within the hexanucleotide mix at least one nucleotide sequence that could hybridize wholly or in part with the sequence of SEQ ID No. 1 and SEQ ID No. 4. Claims 3 and 5 encompass the nucleotide sequence of claim 2; therefore, they are rejected for the same reason.

12. Claims 2, 3, 5 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Mierendorf et al. (U.S. patent 5,629,179).

Mierendorf et al. teaches a method and kit for making a cDNA library wherein the kit comprises random octamer oligonucleotides over every possible sequence (see column 7, line 59-column 8, line 6). As mentioned above, Claim 2 recites, "Isolated nucleic acid that encodes a protein, which is functionally identical to a protein that occurs naturally in human keratinocytes... **or** a nucleotide sequence that hybridizes wholly **or in part** with one of these aforementioned nucleotide sequences." Therefore, the claim encompasses any nucleotide sequence that hybridizes to SEQ ID No. 1 or SEQ ID No. 4. Claim 20 recites, "wherein the oligonucleotide includes 8 to 25 nucleotides". Mierendorf et al. teaches a kit comprising every

possible octamer oligonucleotide. Therefore, the kit taught by Mierendorf et al. includes 8mer (i.e. octamer) oligonucleotides which would hybridize wholly or in part to SEQ ID No. 1 and SEQ ID No. 4.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
April 5, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER